

# Digestive Health Center Research & Innovations Committee

Summer 2020

## A Message from NM DHC Research and Innovations Committee Co-Chairs: Eric Hungness, MD and Sri Komanduri, MD

In this issue of the NM DHC Research and Innovations Committee newsletter, we highlight the DHF Grant awardees and their proposals. In addition, in our continuing effort to bring light to the efforts of our Advanced Practice Providers during COVID-19, we have a special section dedicated to their "Call to Action" centered around their experiences and insight. Finally, we have released our DHC comprehensive research database and "Starting Research in the DHC" Toolkit. These resources will provide faculty and trainees with easy access to all studies ongoing within the DHC and a step-by-step playbook for conducting research at NM. While many of our national meetings have been cancelled in 2020, we congratulate all of our faculty and fellows whose research was selected for presentation at DDW and SAGES.

## Digestive Health Foundation Award Summary

*Congratulations to the FY21 Digestive Health Foundation Grant Awardees. The Digestive Health Foundation would like to congratulate the recipients of the research grant awards for 2021. Below are the awards winners' study descriptions. We look forward to the successes of your projects!*

### Molecular Profiling of Scleroderma Esophageal Disease

**Principal Investigator:**  
Marie-Pier Tetreault, PhD



**Co-Principal Investigator:**  
Sara Radecki

Scleroderma is considered an autoimmune disease stiffening of the body's connective tissues of numerous organs leading to stiffening and functional disruptions. More than 95 percent of scleroderma patients develop GI problems, with the esophagus being the most commonly affected organ. Weakening muscle tissue and impairing function, scleroderma esophageal disease can result in complications such as gastroesophageal reflux (GERD), Barrett's esophagus, and/or adenocarcinoma. Despite efforts to better understand the nature of scleroderma in multiple organs, how scleroderma damages the esophagus remains unclear. Consequently, no treatment exists to change the course of scleroderma esophageal disease. Determining the molecular mechanisms underlying the disease process is critical to developing effective therapies. Using a powerful new technology called single-cell RNA sequencing (scRNA-seq), Dr. Tetreault will examine esophageal biopsies from patients with scleroderma esophageal disease. By pinpointing specific molecular changes in this patient population compared to those of healthy patients, her team hopes to identify novel targets for diagnosis and treatment of this complex disease.



### Recent NM DHC Podcasts:

- [Drs. Hanauer and Strong COVID-19: Key Considerations for Gastroenterologists](#)
- [Dr. Hanauer Optimizing Biologic and Conventional Therapies for Inflammatory Bowel Disease](#)
- [Dr. Pandolfino and Bethany Doerfler Treating GERD with Dietary Therapies](#)

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## Pilot study to assess the feasibility and clinical utility of 7-day home and 24-hour ambulatory blood pressure monitoring in liver transplant recipients

### Principal Investigator:

Lisa B. VanWagner, MD, MSc



Liver transplantation extends the lives of many patients with liver failure. Yet, one in three recipients will experience a heart disease event after liver transplant surgery because of immunosuppression causing a high prevalence of cardiovascular risk factors, such as high blood pressure (BP). Decreasing hypertension in these patients could help improve their outcomes. While there are different methods for detecting high BP, some are better than others. Home monitors and portable/wearable 24-hour monitoring devices often best reveal how blood pressure readings relate to daily activities and sleep and provide keener insights into patients' true blood pressure levels than measurements taken in the clinic. Dr. VanWagner's study will involve measuring blood pressure over time in 50 Northwestern liver transplant recipients. Her team will use the office, home, and 24-hour blood pressure measurement approaches to enable interventions to lower blood pressure and prevent dangerous heart disease events after transplant surgery.

### Co-Principal Investigator:

Donald Lloyd-Jones, MD, ScM

## A Study of Intestinal Permeability in Primary Sclerosing Cholangitis

### Principal Investigator:

Josh Levitsky, MD



Primary sclerosing cholangitis (PSC) causes chronic inflammation of the bile ducts and, over time, potential liver failure. What triggers PSC and how it is strongly linked to ulcerative colitis (UC) remains unclear. One theory is that a "leaky gut" allows toxic compounds from the intestines to erroneously enter the liver. Dr. Levitsky's team intends to test this theory by measuring intestinal permeability in PSC patients. Intestinal permeability (leakiness) can be studied by comparing absorption of different simple sugar solutions. Study participants will drink several sugar solutions to compare absorption and elimination in the urine. Researchers anticipate that the sugar levels in the urine will be different between patients with PSC, patients with PSC and ulcerative colitis, and healthy patients. If this occurs, the team will evaluate therapies, such as antibiotics, to assess their impact on the "leaky gut." This project may serve as an initial step toward developing personalized treatment options for patients who currently don't have any therapeutic options—currently a high unmet need in the field of gastroenterology.

### Co-Principal Investigator:

Imran Nizamuddin, MD

## Resources Developed to Aid Research in the DHC

The Research and Innovation Committee has developed two resources to aid in our mission of supporting research across subspecialties. Both of these resources are located on the NM Digestive Health Center team site (NMI) as a functional resource to assist in starting research, and secondly, to showcase and inform providers of current DHC research that is underway.

### Digestive Health Center's "How to Guide" for starting research:

- Details to aid in the processes of; investigator initiated studies, non-sponsored agreements, industry studies, federal foundation and investigator-initiated studies
- Examples of survey, intervention, and data review

### Digestive Health Center's Research List:

- This comprehensive list includes all prospective studies that are currently active by members of the Digestive Health Center
- Please utilize the sort functions to view by date, subspecialty, or provider
- To ensure accuracy, the list will be reviewed by this committee and research teams quarterly

## Digestive Health Foundation Award Summary FY21 *Continued*

### Open-Label Assessment of the Efficacy of Atrantil In the Treatment of Methane-Predominate Intestinal Bacterial Overgrowth.

**Principal Investigator:**  
Darren Brenner, MD



**Co-Principal Investigator:**  
Jennifer Cai, MD, MPH

Intestinal bacterial overgrowth (IBO) occurs when excessive amounts of bacteria build up in the small intestine (which is usually nearly sterile). These bacteria ferment ingested food, producing hydrogen, methane, and carbon dioxide. These intestinal gases can induce GI symptoms, including abdominal pain, bloating, distention, diarrhea, and constipation. Antibiotics often help, but for some patients, disruptive digestive symptoms will persist. IBO is subcategorized into two types: 1.) small intestinal bacterial overgrowth and 2.) intestinal methanogenic overgrowth. Recent studies suggest that increased methane production may come from the overgrowth of a specific type of bacteria. No current therapies exist to treat methane predominate IBO. An initial study of the herbal supplement Atrantil has shown promise. Investigating the potential benefit of this “holistic” treatment, Dr. Brenner will conduct a trial of Atrantil in 30 patients at the Northwestern Medicine Digestive Health Center. Researchers will evaluate Atrantil’s impact on reducing methane levels, lessening symptoms, and enhancing quality of life. The team believes Atrantil could offer an inexpensive and safe treatment for IBO.

### Critical role of p53 gene mutation in ulcerative colitis-driving carcinogenesis

**Principal Investigator:**  
Guang-Yu Yang, MD



**Co-Principal Investigator:**  
Stephen B. Hanauer, MD

Chronic inflammation is an important risk factor for cancer. Patients with ulcerative colitis (UC) face a significantly increased risk of developing colorectal cancers. Damaged DNA and genetic alterations can be caused by the inflammatory process. Identifying crucial inflammation-associated molecular events offers potential targets to predict and prevent cancers. Missense p53 mutations are one of the most common and earliest molecular events seen in UC-associated carcinogenesis. Yet little is known about the evolution of p53 mutations during the long-term course of UC and whether targeting these mutations will have an impact on the long-term cancer risk in patients with UC. Employing a next-generation sequencing approach, Dr. Yang’s study aims to determine the mutation spectrum and load of the p53 gene in this patient population. The researchers intend to identify whether specific p53 mutations are critical in driving UC-induced carcinogenesis, and to evaluate its role as an efficient biomarker for predicting the risk of cancer development in UC patients.

### Validation of the utility of TCR Sequencing in adults with Eosinophilic Esophagitis for identification of specific food triggers

**Principal Investigator:**  
Joshua Wechsler, MD



**Co-Principal Investigator:**  
Nirmala Gonsalves, MD

Eosinophilic esophagitis (EoE) is an allergic inflammatory disease of the esophagus. Specific foods can trigger esophageal inflammation leading to pain, difficulty swallowing and malnutrition. Elimination diets remain a mainstay for identifying triggers since effective biomarkers or testing are currently nonexistent in this chronic disease. Previous work of Dr. Wechsler’s team revealed an immune response of white blood cells (T-cell receptors) in patients with active EoE who underwent rigorous dietary elimination and reintroduction regimens. Pursuing this promising line of research, Dr. Wechsler intends to examine esophageal biopsies for evidence of the specific immune response of white blood cells to specific foods. The investigators will use deep sequencing of the T-lymphocyte receptor to identify how frequently certain types of T-cells exist between adults with similar and unique food triggers. Findings from this study could open the door to building a digital library of T-cell receptors that identify specific foods and allow for more personalized therapy.

## Digestive Health Foundation Award Summary FY21 *Continued*

### Role of mast cells and IgE in Eosinophilic Esophagitis patients with food induced response of the esophagus (FIRE)

**Principal Investigator:**  
Joshua Wechsler, MD



**Co-Principal Investigator:**  
Ikuo Hirano, MD

An allergic/immune condition, the inflammatory process of eosinophilic esophagitis (EoE) leads to chronic swallowing problems and food impaction. These symptoms develop when large numbers of white blood cells called eosinophils build up in the inner lining of the esophagus. EoE is on the rise in the United States, contributing to more than \$1.4 billion in health care costs annually. Recently, EoE patients have been found to experience abrupt food-induced responses of the esophagus (FIRE). Symptoms occur immediately after the ingestion of foods that don't typically trigger eosinophilic inflammation. Preliminary data from Dr. Ikuo Hirano of the Northwestern Medicine Digestive Health Center suggests these patients are sensitized to specific allergy-related antibodies directed at FIRE-associated foods. An antibody linked to food allergies, IgE typically involve mast cells—immune cells present within tissues such as the esophagus that are increased in patients with EoE. Dr. Wechsler's study will examine esophageal biopsies to determine whether IgE is present on mast cells and whether increased IgE+ mast cells are increased in patients with FIRE when compared to those without FIRE symptoms.

### Additive Value of Wide-Area Transepithelial Sampling (WATS3D) in Detection of Recurrence of Intestinal Metaplasia Following Endoscopic Eradication Therapy (EET) for Barrett's Esophagus-Related Neoplasia

**Principal Investigator:**  
Sri Komanduri, MD, MS,  
FASGE, AGAF



**Co-Principal Investigator:**  
Domenico Farina, MD

Esophageal cancer is a deadly and increasingly common disease in the United States. Up to 15 percent of patients with gastro-esophageal reflux disease (GERD) will develop Barrett's esophagus (BE), a pre-cancerous state that can develop into esophageal cancer. While BE is highly treatable, the progression to esophageal cancer still commonly occurs due to missed detection and diagnosis of Barrett's esophagus, which often returns despite treatment. A new technology, Wide-Area Trans-Epithelial Sampling (WATS-3D), may offer improved detection of abnormal cells (dysplasia) in Barrett's. WATS-3D uses brush sampling to examine larger areas of the esophagus than is achieved in conventional biopsies. Preliminary studies show improved detection of cancerous changes in Barrett's esophagus surveillance. Dr. Komanduri's team hopes to determine if the addition of WATS-3D increases the rate of detection of recurrent Barrett's following treatment. If so, this could be a game changer for patients, allowing for earlier re-treatment of Barrett's and, ultimately, for the prevention of esophageal cancer.

### Functional analysis of ONECUT2, a novel transcriptional regulator of pancreas tumor formation and malignancy

**Principal Investigator:**  
Beatriz Sosa-Pineda, PhD



Pancreatic cancer has one of the worst survival rates in the world, and patients have very limited therapeutic options to fight the disease. It is predicted that close to 47,000 Americans will succumb to pancreatic ductal adenocarcinoma (PDAC) in 2020. Meeting the dire need for new therapies and diagnostic methods requires a better understanding of the fundamental biology of PDAC. Learning more about the molecular mechanisms that govern tumor formation, progression, and spread (metastasis) is critical to improving outcomes. In this study, Dr. Sosa-Pineda intends to build on her lab's previous findings to firmly establish the role of a new gene regulator, the transcription factor ONECUT2, in the development of pancreatic cancer. This project will use molecular approaches to abolish the expression of ONECUT2 and test its effect on pancreatic tumor function. The Sosa-Pineda team will employ additional approaches to identify specific pathways and functions regulated by ONECUT2 in pancreatic tumors.

## Digestive Health Foundation Award Summary FY21 *Continued*

### A Missing Piece of the Puzzle: Patient and Provider Perspectives on Opioid Use and Pain Management in Inflammatory Bowel Disease Care

**Principal Investigator:**  
Jonah Stulberg, MD



**Co-Principal Investigator:**  
Salva Balbale, PhD

The national opioid crisis continues to adversely affect millions of lives, including a growing number of individuals with inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis. Studies have suggested that long-term opioid use among IBD patients can result in serious detrimental effects on GI function. Opioid use disorders in this population have also been linked to longer hospital stays, increasing health care costs, and deaths. Yet a comprehensive understanding of the opioid usage and pain management needs of these patients remains elusive. Additionally, no published studies have explored the decision-making process that IBD providers use when prescribing opioids. Dr. Stulberg's study will lay the groundwork for developing best practices to optimize the use of opioids for IBD patients. The researchers will conduct interviews with IBD providers, in addition to focus groups with IBD patients to ensure all voices are heard and incorporated in future opioid safety efforts to enhance the care and pain management for patients with inflammatory bowel disease. (Dr. Stulberg led a previous DHF-funded study in 2017 that tracked and greatly reduced opioid prescriptions and risk of misuse in GI surgery patients.)

### The Unfolded Protein Response in Liver Transplant Patients with Cholestasis

**Principal Investigator:**  
Xiaoying Liu, PhD



**Co-Principal Investigator:**  
Josh Levitsky, MD

The term cholestasis describes any condition that impairs normal bile flow from the liver into the bile ducts and then into the intestine. This disease state can cause chronic liver damage, cirrhosis, end-stage liver disease (requiring a liver transplant), and death. Cholestatic liver diseases include primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC). Cholestasis also occurs frequently after liver transplantation, which can result in the need for repeat liver transplantation or death. Unfortunately, the molecular drivers of cholestasis are still poorly understood with few effective medical therapies. The liver unfolded protein response (UPR) is a molecular pathway that protects cells from injury. UPR has been demonstrated to be important in many liver diseases, although its role in cholestasis remains unknown. Dr. Liu intends to investigate the activation of the liver UPR pathways in liver transplant patients with cholestasis. Identifying new UPR protein and gene targets will ultimately aid in developing novel drug therapies and improving liver transplant outcomes.

### Use of Endoscopic Functional Lumen Imaging Probe and Antroduodenal Manometry in Predicting Clinical Response to Gastric Peroral Endoscopic Myotomy

**Principal Investigator:**  
A Aziz Adam, MD



**Co-Principal Investigator:**  
Jennifer Cai, MD, MPH

Gastroparesis is a debilitating condition that can cause persistent nausea, vomiting, and abdominal pain due to delayed stomach (gastric) emptying. The inability to eat or drink can lead to malnutrition and reduced quality of life. Current treatments are limited in both effectiveness and durability. A minimally invasive endoscopic procedure called G-POEM has recently shown promise in improving spasms of the sphincter muscle that prevent proper gastric emptying. G-POEM involves cutting this smooth band of muscle—that connects the stomach to the small intestine—to prevent further spasms and to allow the stomach to empty. Dr. Cai hopes to identify which gastroparesis patients would most likely benefit from this treatment using two novel methods: EndoFLIP, a probe that measures sphincter flexibility and antroduodenal manometry (ADM), a catheter that measures pressures throughout the upper gastrointestinal tract. Her team will look for specific EndoFLIP and ADM metrics that can be used to more effectively select patients for and predict improvement after G-POEM.

## Digestive Health Foundation Award Summary FY21 *Continued*

### The role of the unfolded protein response (UPR) in pediatric cholestatic liver diseases

**Principal Investigator:**  
Alyssa Kriegermeier, MD



Children with liver disease frequently suffer from jaundice caused by the poor flow of bile from the liver to the intestines—a disease state called cholestasis. Currently no treatments are available that effectively prevent liver failure due to pediatric cholestatic liver diseases. Lifesaving liver transplantation is often the only answer. Cells within the liver deal with the stress from cholestasis via stress-induced pathways known as the unfolded protein response (UPR). While the UPR has been studied in adult liver diseases, little is known about its activation in children. Dr. Kriegermeier previously demonstrated, in an animal model of primary sclerosing cholangitis (PSC), one form of cholestatic liver disease affecting children and adults (about 80 percent of whom also have inflammatory bowel disease (IBD- Crohn's disease, ulcerative colitis, etc.)), that removing parts of the UPR affects disease progression. This study will seek to better understand the differences in adults and children within this cell stress response during times of cholestasis. Identifying new therapeutic targets will provide a springboard for developing treatments for these children that will hopefully prevent them from needing liver transplantation.

## Advance Practice Providers' Call to Action: COVID 19

*Since the start of the COVID-19 pandemic, many of our providers have been called upon to volunteer within and outside of our department to support our colleagues and patients. Below are a few experiences:*



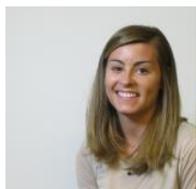
**Brittany Leano PA-C, Inpatient Colorectal Surgery"**

"During this time of crisis, I volunteered to help on the COVID-19 hospital medicine service. Although I am used to functioning on an inpatient service, it was interesting to step out of my surgical role and see how the hospitalist functions. I found there were certain tasks that required additional coordination since the start of the pandemic, such as arranging discharge medications and instructions. Not only did we have to ensure patients' safety, but the safety of others who may potentially be interacting after discharge. I appreciated being a part of the multidisciplinary team during this time. There were a number of teams that came together to put patients first and tackle the pandemic head on. Everything seemed to be discussed from the latest updates on how to manage daily treatments, research studies that were currently happening, and flagging which patients may need to be elevated to a higher level of care. I think these rounds were a great demonstration of how we came together in a time of crisis to do what was best to be better."



**Amber Neal PA-C, Outpatient Colorectal Surgery:**

"I was glad to be able to contribute to the efforts to fight COVID at NM. During the upswing of the outbreak, the outpatient Colorectal Clinic was closed to all but urgent on site visits; affording me the ability to lend my time to the hospital's inpatient COVID units. The teamwork and cohesion with which those units were operated were impressive. Despite treating many very ill patients with a highly contagious novel disease in the setting of a global pandemic, the attending doctors, APPs, nurses, and social workers I encountered were incredibly patient and helpful as this outpatient surgery APP navigated inpatient medicine for the first time. Beyond that, and more importantly, I'm sincerely proud of the care and compassion I saw given to those patients, particularly with nurses and providers at increased personal risk and an under a new, collective sort of distress. I was happy to be able to support their important work in whatever ways they needed."



**Kate Hanley PA-C, Interventional GI:**

"With the help of our GI fellows to cover the interventional GI inpatient service, I was able to spend several days per week supporting our hospital medicine colleagues on the COVID units functioning as a hospitalist APP. During the first couple weeks in March, the preparedness and clam manner of the hospitalist service and bedside RNs were impressive and motivational. The hospitalist team rounded daily with ID, social work, ethics, palliative care and the MICU to support each COVID positive admission. Although seeing COVID patients can be intimidating, the support of all these individuals and the knowledge they have gained through treating

these patients everyday throughout this crisis has made this “new normal” less scary. I cannot thank them enough for the work they have done to support our patients during this time and was happy to have spent time as part of their team.”



**Kaitlin Fiore APN, CNP, Bariatric Surgery:**

“Since early on in the pandemic, I have been assisting with the COVID Monitoring Program. Time spent in this endeavor involved calling patients daily to assess their current symptoms, triage severe symptoms to a local ER or their PCP for further follow up and “graduating” patients from the monitoring line when they reached symptomatic improvement and met CDC and IDPH guidelines to discontinue home isolation. These calls also worked closely with the COVID Social Work team to help patients find answers to non-medical but deeply important issues; such as finding shelter during required quarantine, food insecurity, financial hardship, emotional support and other issues. The team is comprised of over 600 nurses, medical students, APPs, and physicians from every corner of the NM system to put patients first every day. The experience has been humbling, challenging, and rewarding, but most importantly, these calls, for the most part, were so deeply appreciated by patients who were sick, and scared, and often alone. These calls were often their only connection to the outside world. So many patients felt safer knowing that SOMEONE would be calling them every day to check in, and that really made a difference in their health and recovery.”



**Katie Ross PA-C, Nutrition Support:**

“I am proud and fortunate to be part of an unanticipated but revolutionary use of technology as a member of the COVID phone lines at Northwestern. At a time when I physically cannot look a patient in the face, the utilization of telemedicine allows for a meaningful patient connection. I never anticipated having such a strong or emotional rapport with patients who are not tangibly in front of me.”



**Sarah Anderson MS, APN, Hepatology:**

“I have been assisting Corporate Health with notifying NM faculty and staff who have tested positive for COVID. While the focus of our calls is quarantine and return-to-work protocols, I have been moved by the courage of our employees when they're given the disconcerting news. Some have cried, some have expressed anxiety, and many have simply sighed and said they expected their results would be positive; but all have been determined to recover, and to ensure that they help prevent further spread of the infection.”



**Mary Rouzer DNP and Allie Moser FNP-BC, Hepatology:**

“There is a strong sense of camaraderie amongst advanced practice providers (APPs) in the DHC and this sentiment holds true for hepatology. Our group of hepatology APPs has always collaborated and supported one another in order to provide excellent patient care. So it came as no surprise that we were able to work together in order to quickly formulate a plan to cover both inpatient and outpatient hepatology needs during the COVID-19 crisis. For the last two months, Hazel Domingo, PA-C, has been working on the inpatient hepatology service while Mary Rouzer, DNP, and I (Allie Moser, FNP-BC) have covered the outpatient APP responsibilities. Mary and I have worked as a team to ensure that Hazel's patient care is not jeopardized during this time by taking over her tele-visits, follow-up care, and EPIC inbox responsibilities. Although we have been working apart during this unique time, we have drawn closer as a team which undoubtedly has strengthened our hepatology APP team now and into the future.”



**Hazel Domingo PA-C, Hepatology:**

“Collectively, the DHC advanced practice providers were ready and willing to serve in any way we can during this crisis. Now more than ever, we are called to practice at the top of their education and training to utilize their full skillset when patients need them most. While the residents were reassigned to the inpatient COVID19 units, I had the unique opportunity to team up with the transplant hepatology fellows to care for the patients in the inpatient transplant hepatology service. As a physician assistant, my license, experience and training have given me the ability to seamlessly transition from an outpatient to inpatient role. Not only was I able to provide assistance to my team during this critical time, the experience also enriched my practice and allowed me to learn and grow as a provider.”